



Tuberculosis in Cape Town: An age-structured transmission model

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ABSTRACT

Background: Tuberculosis (TB) is the leading cause of death in South Africa. The burden of disease varies by age, with peaks in TB notification rates in the HIV-negative population at ages 0–5, 20–24, and 45–49 years. There is little variation between age groups in the rates in the HIV-positive population. The drivers of this age pattern remain unknown.

Methods: We developed an age-structured simulation model of *Mycobacterium tuberculosis* (Mtb) transmission in Cape Town, South Africa. We considered five states of TB progression: susceptible, infected (latent TB), active TB, treated TB, and treatment default. Latently infected individuals could be re-infected; a previous Mtb infection slowed progression to active disease. We further considered three states of HIV progression: HIV negative, HIV positive, on antiretroviral therapy. To parameterize the model, we analysed treatment outcomes from the Cape Town electronic TB register, social mixing patterns from a Cape Town community and used literature estimates for other parameters. To investigate the main drivers behind the age patterns, we conducted sensitivity analyses on all parameters related to the age structure.

Results: The model replicated the age patterns in HIV-negative TB notification rates of Cape Town in 2009. Simulated TB notification rate in HIV-negative patients was 1000/100,000 person-years (pyrs) in children aged <5 years and decreased to 51/100,000 in children 5–15 years. The peak in early adulthood occurred at 25–29 years (463/100,000 pyrs). After a subsequent decline, simulated TB notification rates gradually increased from the age of 30 years. Sensitivity analyses showed that the dip after the early adult peak was due to the protective effect of latent TB and that retreatment TB was mainly responsible for the rise in TB notification rates from the age of 30 years.

Conclusion: The protective effect of a first latent infection on subsequent infections and the faster progression in previously treated patients are the key determinants of the age-structure of TB notification rates in Cape Town.

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1. Introduction

The HIV and Tuberculosis (TB) epidemics in South Africa (SA) are among the worst in the world. Tuberculosis (TB) is now the leading cause of natural death in South Africa (Statistics South Africa, 2014a). HIV positive individuals who are infected with *Mycobacterium tuberculosis* (Mtb) have a substantially higher risk

of developing active TB than their HIV-negative peers (Corbett et al., 2003), whose lifetime risk following a single infection is about 10% (Styblo, 1991). Even though South Africa has implemented the World Health Organization (WHO) “Directly observed therapy, short course” (DOTS, WHO, 1996) strategy, the incidence of TB in South Africa has continued to rise steadily over the past 20 years, and reached a rate of 1000 cases per 100,000 person-years in 2012 (WHO, 2013). DOTS has been estimated to reduce TB incidence by 11% per year (Dye et al., 1998), but is failing in HIV endemic settings (De Cock and Chaisson, 1999). The HIV-associated TB epidemic partly explains the failure of DOTS to reduce the TB prevalence in SA (Wood et al., 2011b), since about 65% of TB patients in South Africa

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are co-infected with HIV (WHO, 2014a). Because Mtb infection is preventable and TB disease is curable, effective interventions hold the potential of drastically lowering infection and mortality rates.

In addition to DOTS, HIV-specific interventions have been implemented to control TB in this population, including scaling up the use of antiretroviral therapy (ART) and the “Three I’s” strategy: Intensified case finding, Isoniazid preventive therapy (IPT) and infection control (IC) at all clinical encounters (WHO, 2004). Assessing the impact of ART on TB incidence is difficult because ART reduces the risk of TB diseases among HIV-positive individuals and at the same time increases the number of people living with HIV due to reduced HIV-related mortality, thereby increasing the population risk of TB (Bacaer et al., 2008; Bhunu et al., 2009). Mathematical models estimated that universal ART eligibility for all HIV-infected South Africans would reduce the risk of AIDS-related TB by 48% in 2015 (Williams et al., 2010) and reduce new TB cases by 28–37% by 2033 (Pretorius et al., 2014). In contrast, Dodd et al. (Dodd et al., 2013) estimated that TB incidence would initially decline, but rebound 20 years after widespread introduction of ART. Results of modeling studies of IPT are also contradictory. Bacaer et al. (Bacaer et al., 2008) showed that IPT in HIV-positive individuals could substantially reduce TB notification rates. But Mills et al. (Mills et al., 2011) concluded that the predicted effectiveness of IPT would be undermined by repeated re-infections, and Houben et al. (Houben et al., 2014) found that IPT did not cure latent Mtb infection in HIV-positive patients.

TB incidence rates are strongly associated with age (Wiker et al., 2010; Wood et al., 2011a). A study of data from the beginning of the 20th century showed that in the United Kingdom age and reinfection after a cured TB episode were important determinants of transmission (Vynnycky and Fine, 1997). The authors concluded that “the sharp peaks in mortality during young adult life were attributable to the combination of a high incidence of (re)infection and a rapid risk of developing disease in late adolescence”. The same age pattern is also seen today in South Africa: a community-based study in Cape Town, showed that the highest burden of TB had shifted from the oldest (>60 years) age group to a younger population (20–39 year olds) (Lawn et al., 2006). In another study, a very distinct age pattern with three notification peaks at ages 0–5 (first peak), 20–24 (second peak), and 45–49 years (third peak) was observed in the HIV-negative population, whereas in the HIV-positive population the burden of TB mirrored age-stratified HIV prevalence (Wood et al., 2011a). The same study also found a high burden of TB in patients who were previously treated, with most patients having no history of treatment failure or default (Wood et al., 2011a).

Despite being of such importance in TB epidemiology, most South African TB models (Aparicio and Castillo-Chavez, 2009; Bacaer et al., 2008; Bhunu et al., 2009; Blower et al., 1995; Castillo-Chavez and Feng, 1997; Hickson et al., 2012; Mills et al., 2011; Ozcaglar et al., 2012; Rodrigues et al., 2007; Roeger et al., 2009; Williams et al., 2010) do not include age, or include age only for HIV incidence but not for rates of progression from latent Mtb infection to active disease or Mtb transmission. We chose to model Cape Town because of the high quality of TB notification data, and the high rates of HIV testing. We aimed to explore the drivers underlying the age-patterns in HIV-negative TB notification rates observed in Cape Town in a mathematical model that includes age-stratification and reinfection.

2. Methods

2.1. Setting

We modeled the TB dynamics in the city of Cape Town, where both TB and HIV are endemic. In 2009, the population of the Cape

Town metropolitan area was approximately 3.5 million (Statistics South Africa, 2014b). HIV prevalence was estimated at around 5% of the population, and increasing over time (ASSA, 2011). Both HIV care and TB treatment are provided free of charge in government clinics across the city. ART was introduced in 2004 and has been scaled up since, reaching a coverage of 63% in 2013 (Hermans et al., 2015a). According to the 2009 National TB management guidelines, new TB cases are treated for 6 months and TB cases with a history of previous TB for 9 months (Department of Health, 2009). We used these guidelines in our model, because these were the guidelines that influenced the current TB incidence and age structure.

2.2. Model structure

We developed an individual-based TB transmission model stratified by five-year age groups. We used an individual-based stochastic simulation model because it allowed us to consider details about individual TB progression depending on age and time since infection and to capture the uncertainty of modeling outputs. Individuals were simulated from birth to death using the disease progression model implemented in the R package *gems* (Blaser et al., 2015). We considered the following stages of TB progression: susceptible; exposed (latent infection); active disease; treatment; treatment failure/default; and, recovered/susceptible (Figs. 1 and S1). Individuals latently infected with Mtb could be re-infected by another Mtb strain or progress to active disease. Active TB cases were initiated on treatment at a certain rate. After treatment initiation, patients were cured within six months (nine months in the case of retreatment TB) or they failed treatment. Cured individuals were considered susceptible to new Mtb infections (Marx et al., 2014). In case of reinfection, individuals progressed to active disease at twice the rate as previously uninfected individuals (Wood et al., 2011a).

We modeled HIV status of the patients as HIV-negative, HIV-positive not on ART, and HIV-positive on ART (Figs. 1, S2). We assumed HIV incidence was independent of TB progression, but TB progression depended on HIV status. ART initiation was also independent of the natural TB progression, but patients treated for TB were also initiated on ART. We first modeled HIV status over the entire lifespan and then Mtb infection and progression based on HIV status. We considered heterosexual transmission of HIV but ignored vertical transmission. We used separate HIV incidence rates for the pre-ART and ART eras (Table S1). In addition, each simulated individual had characteristics that changed over time: age, number of previous Mtb exposures, and number of previous active TB episodes.

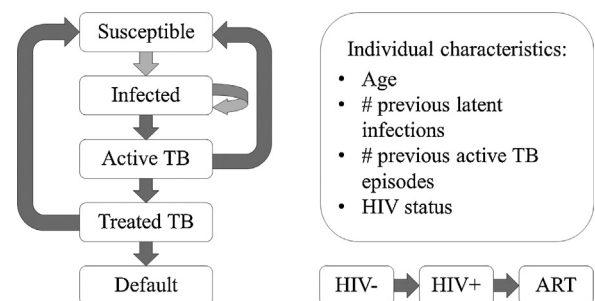


Fig. 1. Model structure. Individuals who start in the susceptible state can be exposed to tuberculosis. Exposed individuals can be exposed to a second strain or progress to active TB. Patients with active TB can recover spontaneously or receive treatment. Treated patients either recover and become susceptible again or they default. Throughout this TB progression, all individuals can also progress in their HIV status, by becoming infected and receiving antiretroviral therapy (ART). Even though it is not represented on the diagram, patients can die at any of the stages.

Table 1
Parameter description and values for all model parameters.

Parameter description	Depended on	Stratification	Value	95% CI	Source
Progression from exposed state to active TB (rate per year)	Time since infection	Age ≤ 5	0.24	NA	Smith (2001)
Rate ratios for progression to active TB		5 < age ≤ 10	0.02	NA	Ferebee (1970)
		10 < age	Fig. S4		
		HIV-positive (vs. HIV-negative)	6	3.5–8	Corbett et al. (2003)
		ART (vs. no ART)	0.50	0.37–0.72	Gupta et al. (2012)
		Reinfection with additional strain (HIV-negative only)	0.21	0.14–0.3	Andrews et al. (2012)
TB treatment rate per year		Reinfection after treatment	2	2–3	Wood et al. (2011a) and Den Boon et al. (2007)
		HIV-, smear+	1.52	NA	
		HIV-, smear-	0.15	NA	
		HIV+, smear+	0.47	NA	
Spontaneous recovery rate per year		HIV+, smear-	0.23	NA	
		HIV-	0.25	NA	Bacaer et al. (2008) from Corbett et al. (2003) and Murray et al. (1990)
TB treatment outcomes	Age (in 5-year groups), HIV status	First treatment vs. retreatment	Table S2/S3, Fig. S6		Data analysis from Cape Town metropolitan electronic TB register
Proportion of smear+	age	HIV-negative	Table S1		Wood et al. (2011a)
HIV incidence	age	HIV-positive			
ART initiation (for time period where ART was available)		Time period (pre-HIV, HIV and ART available)	Table S1		ASSA model (ASSA, 2011)
		No TB treatment	0.13	0.08–0.29	Wandel et al. (2008)
All-cause mortality rate (non-HIV, non-TB)	age	TB treatment	1.27	1.24–1.30	Kaplan et al. (2014)
			Table S1		ASSA model (ASSA, 2011)
Mortality rate ratio due to untreated active TB			17.1	16.8–17.3	Drolet et al. (1952)
Mortality rate ratio for HIV-related mortality	age		Table S1		Sewankambo et al. (2000)
Mortality rate ratio for mortality on ART	age		Table S1		Johnson et al. (2013)
Transmission rate per year			10	6–15	Fit to TB notification rates
Age-specific mixing	age		Fig. S3		Wood et al. (2012) reanalysis
Case detection proportion		age > 16	73%		WHO (2014b)
		age ≤ 15	35%		Dodd et al. (2014)

2.3. Model parameters and data sources

We used data from the literature and performed dedicated analyses of existing data. HIV incidence rates to parameterize the model, disease progression rates, treatment outcomes (cure, failure) and mortality rates were assumed to depend on age. In HIV-negative children below the age of 5 years, and between 5 and 10 years, we assumed constant TB disease progression rates regardless of the duration of infection. For older HIV-negative individuals, disease progression rates depended on the time since Mtb infection: we fit an exponential decay to the progression rates reported in Ferebee et al. (Ferebee, 1970) (Fig. S4). Individuals who were latently infected and re-infected with another strain of Mtb had partial protection and progressed from latent to active TB at a rate 0.21 times lower than that of previously uninfected individuals (Andrews et al., 2012). To determine disease progression rates for HIV-positives with and without ART, we applied age-dependent rate ratios to the parameter estimates from the HIV-negative population (Johnson et al., 2013; Sewankambo et al., 2000). Age-specific mortality rates were also determined for HIV-negative people without active TB. We extracted age-specific all-cause mortality rates from the Actuarial Society of South Africa (ASSA) model for the Western Cape (ASSA, 2011). Then we used rate ratios to calculate mortality rates by HIV status and TB status. We extracted age-specific HIV incidence rates for the pre-ART era and for the ART-era from the ASSA model for the Western Cape (ASSA, 2011).

We reanalyzed data from a survey in a semi-urban community in Cape Town (Johnstone-Robertson et al., 2011; Wood et al., 2012) to

determine age-specific mixing patterns. During a 24-h period, 571 randomly selected participants were asked to keep a diary of their indoor contacts and the time spent in each of the following indoor locations: community buildings, crèches/schools, transport, work, household, and other indoor locations. We calculated the average time of close contact of the contacting age group with each other age group. We used this total time spent with other age groups together with the transmission rate per time spent together to calculate the number of new infections.

We analyzed data from the Cape Town metropolitan electronic TB register (ETR), which includes data on all TB cases notified in the city from 2003 onwards to obtain estimates for TB treatment outcomes. Case fatalities were all deaths occurring during treatment; defaults included both treatment failures and stopped treatment. We report the point estimate and the 95% confidence intervals. The University of Cape Town Research Ethics Committee considered these analyses exempt from ethical review as the data used was routinely collected, anonymized, and in aggregate.

We incorporated parameter uncertainty into the model by sampling disease progression rates for each patient from a multivariate log-normal distribution. Table 1 shows the parameter values and confidence intervals that we used for the final model. The overall Mtb transmission rate of the model was fitted to TB notification rates in Cape Town from 2009 (Wood et al., 2011a). We initialized the model with 80% susceptible individuals; 20% of the randomly selected individuals were latently infected with Mtb at time zero, and most of them never developed active disease. Median age at initialization was 30.4 years (interquartile range:

14.5–50.1); 17.3% of individuals were HIV-positive. These numbers were the values that the model converged to after starting from different arbitrary values. Assuming that TB does not affect age-structure and HIV incidence, the age-structure and HIV prevalence should stay roughly the same when introducing TB into the model. We modeled temporal trends in the HIV epidemic, by splitting time into a period before the HIV epidemic (1950–1984), a period with HIV and no ART (1985–2004) and a period when ART was available (2005 onwards). Except for the HIV-related parameters we used current parameters instead of trying to estimate all parameters for each of the periods separately.

2.4. Model update

We modeled a population with a constant size of 10,000 individuals. The population was updated at monthly time-steps as individuals aged and progressed through disease stages. At each time-step, we determined the Mtb transmission potential by 5-year age group. We counted the number of people with active TB and multiplied this by the proportion of smear positive TB cases in an age-group. We calculated age-specific TB incidence rates (in 5-year age-groups) from the age-specific transmission potential, using the age-specific mixing patterns observed in the semi-urban community. All individuals without active TB or TB treatment were considered susceptible to new TB infection. For newly infected individuals, time of death and all other possible event times were simulated again, using the disease progression model *gems* (Blaser et al., 2015).

2.5. Model output

The main model outcomes were age-stratified notifications of active TB disease for HIV-negative and HIV-positive individuals. We assumed that 73% of incident TB cases were notified in adults (WHO, 2014b) and 35% in children (Dodd et al., 2014). At each time-step, we recorded the number of individuals in each disease stage stratified by 5-year age groups. Using these data, we plotted annual TB incidence and prevalence rates to determine convergence from the initial values. After convergence, we plotted the average and 95% confidence interval of active TB notifications by 5-year age group. We also compared demographic outputs such as HIV prevalence, ART coverage and age distribution to the observed demographics.

2.6. Sensitivity analyses

We conducted sensitivity analyses for all parameters related to the age-structure to investigate the main drivers of the age-pattern. We varied age-specific mixing patterns and age-specific HIV incidence rates. We used extreme parameter values (random mixing, only modeling the HIV-negative population) to determine their influence on the model output. We also did a sensitivity analysis of TB progression rates in retreatment TB cases assuming that TB progression was the same in cases reinfected after prior treatment and in primary cases. We conducted an analysis assuming that latent Mtb infection did not have any protective effect on the progression of future infections. We also looked at model outcomes before HIV was introduced into the population and before ART was introduced into the population to determine the impact of HIV and ART on the age structure of TB. We conducted further sensitivity analyses assuming a lower case detection rate in older individuals and assuming that previously treated patients had a higher mortality risk.

3. Results

3.1.1. Data analyses and model parameters

Of 103,304 new cases of tuberculosis notified between 2003 and 2012, 4.3% died (case fatality rate), 9.4% failed or stopped treatment (default), and 86.3% completed treatment or were cured. Of 41,132 retreatment TB cases, 7.3% died, 19.4% failed treatment and 73.3% completed treatment or were cured. The case fatality rate increased with age for both new and retreatment TB. Treatment outcomes are shown separately for each age group and HIV status in Table S2 for primary disease and in Table S3 for retreatment TB.

Fig. S3 shows the age-specific mixing patterns that we observed in a semi urban settlement and used in the model. We observed some age-assortative mixing, and a noticeable decline in overall indoor contact time spent among older individuals. The 35–40 year olds mixed the most, both with each other and with children aged between 0 and 14 years.

3.2. Model fit

The modeled notification rates of active TB reproduced the shape of the observed age pattern in TB notification rates in 2009, with a drop in TB notification rates around the age of 5 years, a subsequent peak among 20–25 year old adults and an increase in notification rates among 30–50 year old adults. Fig. 2 (upper panel) shows simulated TB notification rates by age group and the TB notification rates observed in the HIV-negative population of Cape Town. Some differences were apparent. A second peak occurred at age 45–50 years in the observed TB notification rates. In the simulated TB notification rates, the increase in TB notification rates continued. In the HIV-positive population, neither the notification data nor the simulations indicated that TB incidence varied by age (Fig. 2 lower panel).

We estimated the overall Mtb transmission rate to be 10 (6–15) per year. The simulation converged to a stable equilibrium within 10 years after model initialization. The notification rates converge to 1,080 per 100,000 person-years within the first few years. It took about 10 years for the prevalence of active TB to converge to 2210 per 100,000 persons. Fig. S5 shows the convergence of prevalence and incidence after simulation start. HIV prevalence at the end of simulation was 11.6% with an ART coverage of 62%. Compared to estimates in the Western Cape this is a higher HIV prevalence than 5.1% (ASSA, 2011) and consistent with ART coverage of 63%. (Hermans et al., 2015a). The age pyramid at the end of simulation was very similar to the 2014 Cape Town age pyramid, with the exception of a higher proportion of children aged 5–20 years (Fig. S9).

3.3. Sensitivity analyses

Fig. 3 shows the results of the sensitivity analyses. The age-specific TB notification rates in HIV-negative individuals for each of the sensitivity analyses are shown. The lines represent the median results and the shaded areas contain 95% of simulations. In Fig. 3a we show the base analysis for comparison. In the scenario without protective effect (Fig. 3b), we assumed that latent infection with a second strain of Mtb did not provide any protective effect on progression to active disease. In the analysis assuming no faster progression after treatment (Fig. 3c), we assumed that TB progression after treatment was exactly the same as the progression for the first TB episode. In Figs. 3d–f we show the sensitivity analyses that made little difference: the analysis assuming no HIV incidence and the analysis assuming random mixing. Figs. 3g and h show the sensitivity analyses that attempt to explain the decline in TB notification rates in the 50 to 80 year old population.

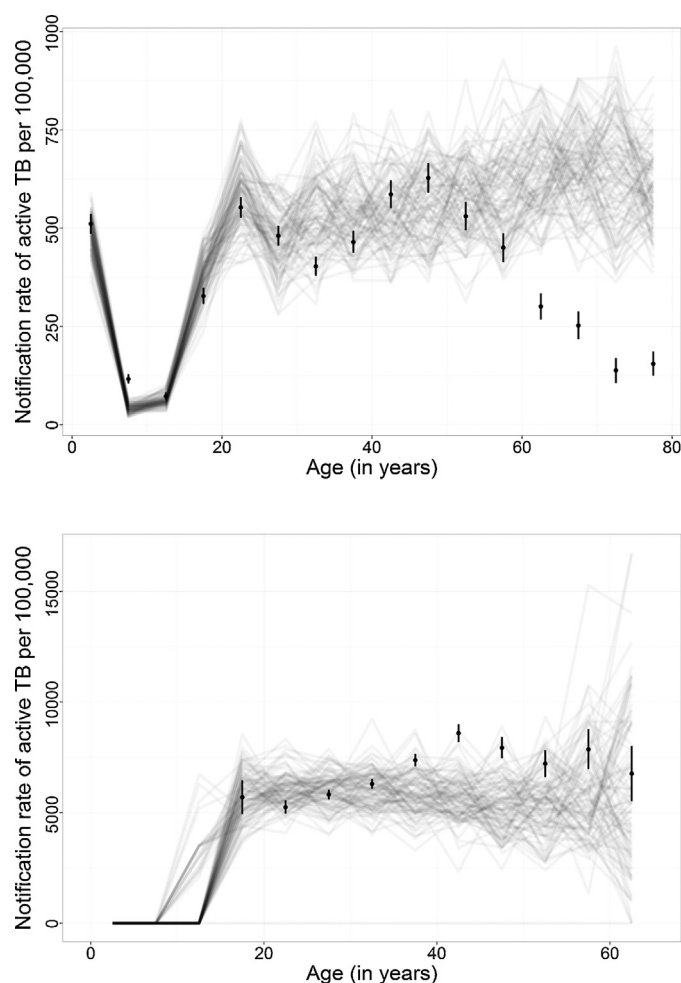


Fig. 2. Age-stratified graph, including uncertainty. The upper panel shows TB notification rates in the HIV-negative population and the lower panel shows TB notification rates in the HIV-positive population. The dots and confidence intervals represent the data reported in [Wood et al. \(2011a\)](#) and the gray lines represent one model run each.

The model was most sensitive to varying assumptions on the protective effect of previous latent *Mtb* strains and to retreatment TB progression rates. The assumption of a protective effect had a large influence on the level of the TB notification rates ([Fig. 3b](#)). When assuming that re-infection with another strain of *Mtb* while being latently infected did not provide any protective effect on progression to active disease, the overall TB notification rate was much higher (1628 per 100,000 person-years) than in the base analysis (451 per 100,000 person-years). Assuming that retreatment TB progression rates were the same as progression rates for primary TB resulted in the TB notification rates in adults decreasing by 35.3%. This decrease was more pronounced (46.6%) among individuals over 50 ([Fig. 3c](#)). The decline in TB notification rates after early adulthood was not seen in the analysis without the protective effect of a previous latent *Mtb* infection ([Fig. 3b](#)). The last peak in adults was absent in the scenario without faster progression to active TB in previously treated patients ([Fig. 3c](#)). HIV incidence had little effect on the age-structure of TB notification rates in the HIV-negative population ([Fig. 3d](#)). Overall TB notification rates increased rapidly from less than 500 notifications per 100,000 person years to around 900 notifications per 100,000 person years when HIV was introduced in the model ([Fig. S7](#)). They decreased slightly to about 700 notifications per 100,000 person years after the introduction of ART. But TB notification rates in HIV negative individuals

of all age groups remained stable throughout the three eras ([Fig. S8](#)). When we assumed random mixing instead of age-assortative mixing, TB notification was essentially unchanged ([Fig. 3e](#)). If we assumed progression rates in children was twice as fast as in our base assumptions, TB notifications in children increased, but the age pattern in adults remained the same.

To explain the lack of fit in 50–80 year old adults we performed additional sensitivity analyses. Having a higher mortality in previously treated patients led to a decline of TB notification rates in older individuals, but it also resulted in a less sharp increase in 30–50 year old adults ([Fig. 3g](#)). A lower detection rate in older individuals seems to fit the observed age pattern well ([Fig. 3h](#)).

4. Discussion

We used a mathematical simulation model to examine the drivers underlying the age-patterns in TB notification rates observed in Cape Town. We replicated the age-structure of TB notifications in Cape Town up to 50 years of age in our model. We found that the first peak in children is likely due to high transmission and rapid progression in children. The second peak is probably explained by relatively rapid progression in early adulthood whereas the increase between 30 and 50 year olds was explained by disease in previously treated patients. Our sensitivity analyses showed that age-specific TB notification rates mostly depended on the protective effect of previous latent infection and the fast progression in previously treated patients. When we assumed no protective effect of previous latent infections, the decline in TB notification rates around the age of 25 years disappeared and TB notification rates remained high in adulthood. This suggests that the decline after the secondary peak in TB notification rates is partially due to a protective effect of latent *Mtb* infection on progression to active TB upon infection with a second strain. The last increase in TB notification rates disappeared in our sensitivity analysis assuming no faster progression to TB disease in previously treated patients, which suggests that this faster progression determines the increased rates in 45–50 year olds. The sensitivity analyses also suggest that the age-pattern observed in the HIV-negative population is not affected by age-specific social mixing patterns or by HIV-associated TB. *Mtb* transmission rates also did not affect TB notification rates as much as might have been expected, perhaps because exposure is saturated and most of those exposed to *Mtb* never develop active TB; additional exposure may not affect TB incidence very much.

In 50–80 year old adults, the model did not reproduce the decline in notification rates observed in the data. This led us to explore additional factors as a possible explanation for the lack of fit. A higher mortality among previously treated patients improved the fit, but a reduced case detection rate in older individuals seemed to fit the observed age pattern the best. However this lower detection incorporated in the model was chosen to fit the age pattern above 50 years. Further research is needed to further elucidate the causes of the declining notification rates at older ages.

Our study has several strengths. We included detailed, time-dependent disease progression rates observed in Cape Town. All parameter values except for the overall transmission rate were extraneously set and parameter uncertainty was included wherever possible. We also conducted detailed sensitivity analyses. There are also several limitations to our model. As outlined above, the model did not fit the age-structured TB notification rates in HIV-negatives perfectly. Since all parameters were set exogenously, we believe that the model fit was good without over-fitting the data. The model did not fit the data well for HIV-positives below the age of 15 and above the age of 40, probably because we did not include mother-to-child transmission of HIV and because of the uncertainty in the denominators in the data. The age distribution

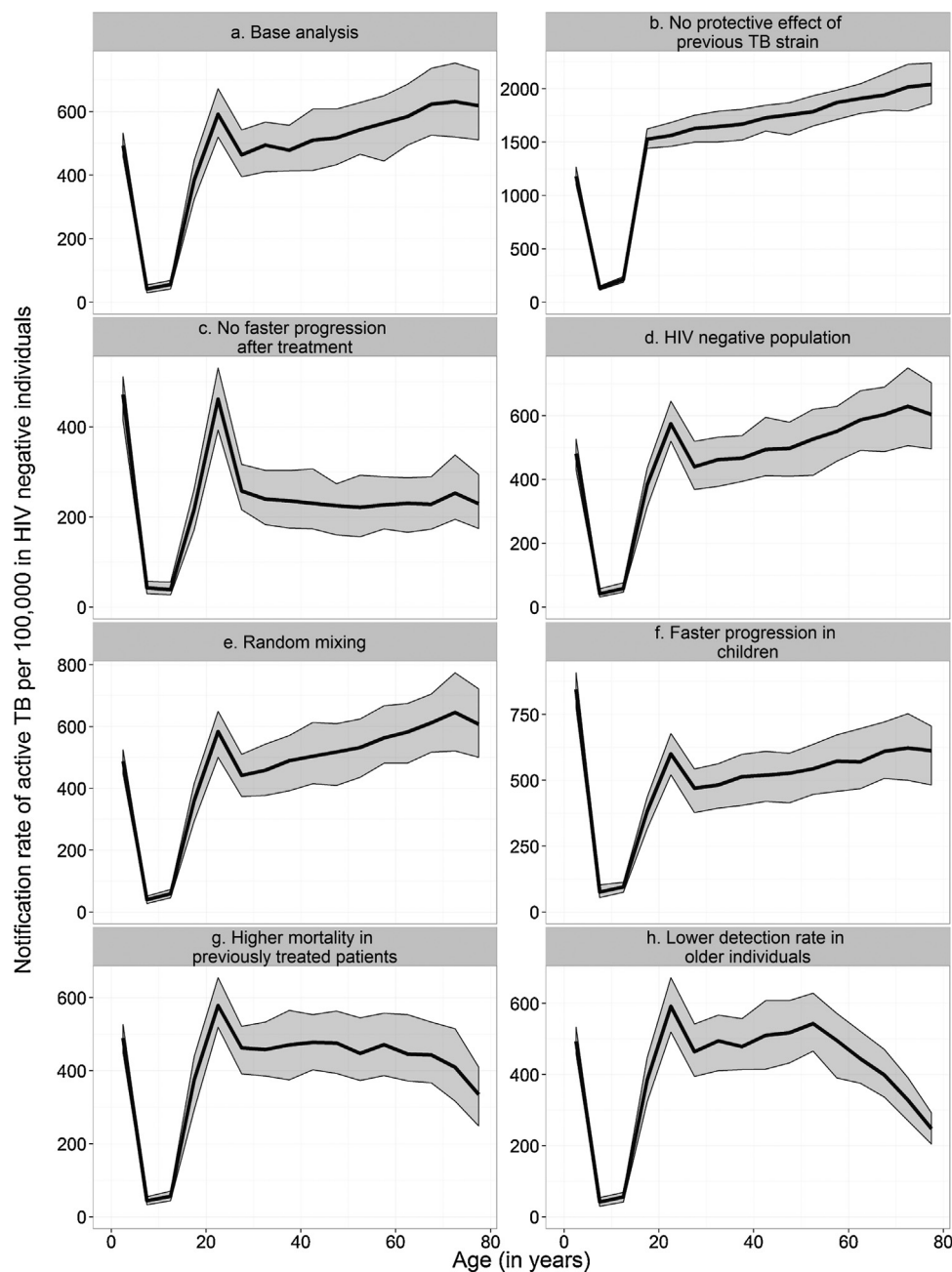


Fig. 3. Sensitivity analyses. The age-specific TB notification rates in HIV-negative individuals for each of the sensitivity analyses are shown. The lines represent the median results and the shaded areas contain 95% of simulations. Panel a shows the base analysis, Panel b shows the analysis without a protective effect of previous TB strains and Panel c shows the results without faster progression after treatment. Panel d shows the analysis in an entirely HIV-negative population. Panel e shows the analysis where we assumed random mixing. Panel f shows the analysis where we assumed children progressed to active TB twice as fast. Panel g shows the analysis where we assumed a higher mortality in previously treated patients and panel h shows the simulation results assuming lower case detection rate in older individuals. Note that the scales on the y-axis differ.

of the simulated population differed slightly from the observed data in Cape Town in children and adolescents (Fig. S9). We also assumed that HIV incidence was independent of TB status (susceptible, latent infection, disease, recovered), even though van Schalkwyk et al. (Van Schalkwyk et al., 2014) suggest otherwise. We used average HIV incidence rates for the pre-ART and ART era, which may have affected TB notification rates in the HIV-positive population. We did not use historical parameters to model the pre-HIV era TB epidemic. We feel that that would have added a lot of uncertainty about the model parameters to our study while adding little information. The most important changes in TB incidence during the last 30 years were due to HIV and the introduction of ART. Since our focus was the age structure in an HIV-negative population,

which remained similar during the last 10 years and was insensitive to HIV, we do not believe that this is a major limitation. Nevertheless, the rates in the pre-HIV and HIV eras we estimated are very similar to historical rates from this setting (Hermans et al., 2015b). A further limitation is that we did not include CD4 cell count of HIV-positive patients in the model. This could have impacted the estimates in the HIV-positive population. Since the focus of this study was on HIV-negative individuals and the HIV infected population did not substantially influence the age structure of TB in HIV-negative people, we think adding CD4 would have added unnecessary complexity to the model. We assumed that all patients who cleared active TB naturally or after being treated successfully became susceptible and uninfected. Some accuracy may have been

lost when we divided the model into discrete time steps. Our age-mixing matrix may have underestimated the contacts of elderly people, because we only used indoor contacts in schools, workplaces, and transport. But this is unlikely to significantly affect our results, since the sensitivity analysis showed that random mixing led to the same age-pattern.

In contrast to the many HIV models in which age-specific prevalence and incidence were used extensively to validate models (Bershteyn et al., 2013; Cambiano et al., 2013), we believe ours is the first mathematical model of Mtb transmission to focus on age-specific TB notifications in sub-Saharan Africa. Although a number of previous TB models were stratified by age (Dye et al., 1998; Schulzer et al., 1994; Stover et al., 2010), they did not compare modeled age-specific TB notifications to available data. For most of them, age-stratification was mainly intended to capture age-specific HIV prevalence. Dodd et al. (Dodd et al., 2014) used a static population model and a household model to estimate the incidence of pediatric TB based on adult notification rates. Vynnycky and Fine (Vynnycky and Fine, 1997) explicitly incorporated age-structure in a TB transmission model, and found that age and reinfections were major factors in the spread of TB in England and Wales, where HIV is not a primary driver of TB. Our results extend their findings to settings with endemic HIV. Our estimate of the overall Mtb transmission rate of 10.0 per year was similar to the estimate of Vynnycky and Fine (Vynnycky and Fine, 1999) for 1950 England. It is also consistent with Bacaer et al. (Bacaer et al., 2008) who estimated a Mtb transmission rate of 11.4 per year in Cape Town.

Our results have important implications for TB prevention and treatment programs. Our model results suggest that TB interventions, such as DOTS, TB screening, IPT, and ART in HIV-infected TB patients should take age into account. IPT and case finding may be particularly important in young adults considering the rapid progression rates in early adulthood. Similarly, new prevention programs could target case finding at previously treated patients aged 40–50 years. Focusing interventions on the most at-risk age groups may increase their effectiveness (Lawn et al., 2006). More research is needed to determine the implications of the age-dependent progression rates on TB control.

In conclusion, by including age strata, we were able to replicate the age-structure of TB incidence in Cape Town up to 50 years of age. More research is needed to determine the causes for declining TB notification rates with increasing age. The protective effect of a first latent infection on subsequent infections and the faster progression to disease among previously treated patients are the key factors in explaining the age-structure of TB incidence in Cape Town.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.epidem.2015.10.001](https://doi.org/10.1016/j.epidem.2015.10.001).

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